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Journal of General medicine and Clinical Practice

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Research Article

Characteristics and Vaccine Booster Effectiveness in Covid-19 Infections Using 15 Days Post-Booster Period as Baseline during the Omicron Wave in A General Medicine office in Toledo (Spain)

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Received Date: April 21, 2022; **Accepted Date:** May 20, 2022; **Published Date:** June 21, 2022.

Citation: Jose Luis Turabian, (2022) Characteristics and Vaccine Booster Effectiveness in Covid-19 Infections Using 15 Days Post-Booster Period as Baseline During the Omicron Wave in A General Medicine Office in Toledo (Spain). *J. General medicine and Clinical Practice*, 5(2); DOI:10.31579/2639-4162/050

Abstract

Background: Vaccine covid-19 booster effectiveness (VBE) timing is not clearly known

Objective: To compare the cases of covid-19 in vaccinated booster people with a time of <15 days vs. >= 15 days from booster to infection diagnosis and assess their relative VBE.

Methodology: An observational, longitudinal and prospective study of adult patients with covid-19 breakthrough infections in booster vaccinated people, in general medicine and for the period December 2021 to February 2022, during the omicron variant contagion wave.

Results: Forty-six cases were included, 15 cases of Covid-19 breakthrough infections with booster shot <15 days (33%) with a mean time in days from booster to diagnostic covid-19 of 6 days, and 31 cases with booster > = 15 days (67%) with a time in days from booster to covid-19 diagnostic of 37 days of mean. Relative VBE <15 days (cases where it can be considered that the booster is not yet effective) vs. > = 15 days (cases where it can be considered that the booster is already effective) [1 - (Cases with vaccine Booster shot < 15 days) / (Cases with vaccine Booster shot > = 15 days) x 100] was 60%. Covid-19 cases with booster shot <15 days had been more vaccinated with 2 doses of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) plus booster of mRNA-1273 vaccine (Spikevax, formerly covid-19 Vaccine Moderna).

Conclusion: In the general practice setting in Toledo, Spain, from December 1, 2021 to February 28, 2022, at the peak of omicron infections, booster after a period of <15 days provided 60% relative protection against symptomatic disease vs. > = 15 days. The results suggest that booster received <15 days provided early protection against SARS-CoV-2 infection of symptomatic Covid-19 of 60%. However, this result does not seem logical: this lower early risk may be transient and due to "vaccinated bias."

Keywords: COVID-19; SARS-CoV-2; COVID-19 vaccine; breakthrough infection; immunization, secondary; general practice

Introduction

The introduction of vaccines against coronavirus disease 2019 (covid-19) marked a turning point in the pandemic, and many lives have been saved thanks to them, reducing illnesses and hospital admissions [1-3]. From the extension of the covid-19 vaccination in December 2020 to the end of the summer of 2021, cases of breakthrough Infection in vaccinated people were rare and their attack rate low; But, starting this year, the omicron variant (B.1.1.529) was breaking records for covid-19 infection in Europe, North America, Africa, and Australia [4, 5].

Four vaccines were authorized in early 2022 for use in the European Union to prevent covid-19, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These vaccines include, two messenger RNA (mRNA)-based vaccines (BNT162b2 mRNA vaccine [Comirnaty, Pfizer / BioNTech] and mRNA-1273 vaccine [Spikevax, formerly COVID-19 Vaccine Moderna]), and two adenovirus vector-

based vaccines (ChAdOx1 nCoV-19 vaccine [Vaxzevria, Oxford / AstraZeneca] and Ad26.COV2.S [Johnson & Johnson–Janssen vaccine]). These vaccines have been shown to be highly effective in preventing mild to severe covid-19 [6]. However, decreased vaccine-induced immunity and the emergence of concerning variants of SARS-CoV-2 with increased transmission and resistance to neutralization have limited their efficacy [5, 7-9].

In this way, the rapid increase in covid-19 cases due to the omicron variant of SARS-CoV-2 in highly vaccinated populations raised concerns about the effectiveness of current vaccines. As early as August 2020, documented accounts of reinfection indicated that immunity to SARS-CoV-2 may only transiently protect from infection [10, 11]. Subsequent studies clearly established that vaccine efficacy against infection and symptomatic disease declines over time, so additional doses of vaccine (boosters) may be beneficial [9]. This was quickly followed by the decision to vaccinate with third doses, starting in the fall of 2021, to all people who received the second dose at least 5 months earlier, regardless of age, in an effort to maintain the efficacy of the vaccine over time [4, 12, 13]. There is now data that strongly suggests that people with the triple vaccine are more likely to avoid serious health complications, hospitalizations and deaths [14]. Three doses of the vaccine are required to achieve protection against omicron similar to the protection that two doses provided against the delta and alpha variants [13].

In this scenario, understanding the epidemiology of SARS-CoV-2 variants and the efficacy of existing vaccines is essential to guide vaccination policies and the development of new vaccines [13]. But, real-world data on vaccine effectiveness (VE) against newer SARS-CoV-2 variants remains limited [10]. Especially there is a lack of data on the period of time after the booster (durability of the effect of the third dose), during which the effectiveness of the booster is maintained [15, 16].

In this context, we present this study, where we estimate the relative effectiveness of the vaccine against symptomatic disease, presumably caused based on the time period studied, by delta and especially omicron variants, after two doses (primary immunization) of the vaccine, and after homologous or heterologous booster doses < 15 vs. >15 days.

Material and Methods

An observational, longitudinal and prospective study of covid-19 breakthrough infections in vaccinated people with Vaccine Booster was conducted from December 1, 2021 to February 28, 2022, in a general medicine office in Toledo, Spain, which has a list of 2,000 patients> 14 years of age (in Spain, the general practitioners [GPs] care for people > 14 years of age, except for exceptions requested by the child's family and accepted by the GP). The GPs in Spain work within the National Health System, which is public in nature, and are the gateway for all patients to the system, and each person is assigned a GP [17].

Objective of the study

A. To compare the cases of covid-19 breakthrough infections in vaccinated people with vaccine booster with a time of <15 days vs. > = 15 days from booster to infection diagnosis

B. To evaluate the relative vaccine booster effectiveness (VBE) <15 days vs. > = 15 days.

Criteria for inclusion and exclusion of participants

The methodology of the study has already been published previously [18]. Only cases of patients fully vaccinated with two doses, plus booster, were included.

1. To consider a person as fully vaccinated (primary vaccination), it was required (19):

1. That they have received 2 doses of vaccine separated by a minimum of 19 days if the first dose was BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech), 21 days in the case of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) or 25 days in the case of mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna), and that a minimum period of 7 days has elapsed since the last dose if the last dose was with BNT162b2 mRNA vaccine (Comirnaty), or 14 days if it was with ChAdOx1 nCoV-19 vaccine (Vaxzevria) or mRNA-1273 vaccine (Spikevax). People who received a dose of Janssen vaccine (Johnson & Johnson vaccine) more than 14 days ago were also considered fully vaccinated.

2. Or, that having passed the disease they have received a dose of any of the vaccines, after the minimum period equal to that established for the second doses.

3. In the heterologous regimen in which Vaxzevria (Oxford / AstraZeneca) is used in the first dose and mRNA vaccines in the second, it was considered fully vaccinated after 7 days if the second dose was with Comirnaty, or after 14 days if it was with the Moderna vaccine

2. Definition of homologous or heterologous booster

Currently, the European Commission has authorized four vaccines: Comirnaty, from Pfizer/BioNTech, authorized December 21, 2020; Moderna vaccine, authorized on January 6, 2021; AstraZeneca vaccine, authorized on January 29 and Janssen/Johnson & Johnson vaccine, authorized on March 11, 2021. These four vaccines are currently available in Spain; all of them have been approved by the European Medicines Agency. These vaccines have been shown to be highly effective in preventing mild to severe covid-19 [19]. The original BNT162b2 mRNA vaccine (Comirnaty, Pfizer/BioNTech), mRNA-1273, and ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca) regimens were homologous induction and booster regimens, whereas the original Ad26. COV2.S vaccine (Janssen vaccine; Johnson & Johnson vaccine) was a single injection regimen.

As of November 23, 2021, in Castilla-La Mancha, the region where the study was carried out, booster doses against covid-19 with messenger RNA (mRNA) vaccines began 6 months after completion the vaccination schedule and after 3 months in case of having received a dose of the Ad26.COV2.S vaccine (Janssen vaccine; Johnson & Johnson vaccine). Recruitment was carried out actively by age cohorts in a descending manner, beginning with those over 80 years of age and people inpatients in centers for the elderly and in other socio-health and health centers (including day centers and occupational centers), regardless of age, people who received a dose of Ad26.COV2.S vaccine (Janssen vaccine; Johnson & Johnson vaccine) as primary vaccination and those with a homologous schedule of Vaxzevria as primary vaccination (first and second dose of Vaxzevria, from AstraZeneca), followed by people aged between 79 to 70 years old, from 69 to 65 years old, 64 to 60 years old, 59 to 50 and 49 to 40 years old, etc. The booster dose was administered with mRNA vaccines (0.3 ml of Comirnaty or 0.25 ml of Spikevax – half the usual dose in primary vaccination).

-Homologous or heterologous booster

Any mRNA vaccine was used to administer the booster dose, regardless of the vaccine used in the primary vaccination. In people with incomplete regimen (in vaccines that require two doses as primary vaccination) the regimen was completed first with mRNA vaccine (0.3 ml of BNT162b2 mRNA vaccine [Comirnaty, Pfizer / BioNTech] or 0.5 ml of mRNA-1273 vaccine [Spikevax, formerly covid-19 Vaccine Moderna]). The booster dose (0.3 ml Comirnaty or 0.25 ml Spikevax) was given 6 months later. In people for whom a booster dose was recommended who had a history of symptomatic or asymptomatic SARS-CoV-2 infection, a booster dose with mRNA (0.3 ml of Comirnaty or 0. 25 ml of Spikevax)

at least 4 weeks after the diagnosis of the infection and from 6 months (subsequently modified on January 13, 2022 to 5 months) if the last dose administered in the primary vaccination was with mRNA vaccine (Comirnaty or Spikevax), and from 3 months if it was an adenovirus vector vaccine (ChAdOx1 nCoV-19 vaccine [Vaxzevria, Oxford / AstraZeneca] or Ad26.COV2.S vaccine [Janssen vaccine; Johnson & Johnson vaccine]) [20].

3. To consider a person completely vaccinated with the booster, it was required:

For the data in this study, all covid-19 cases in people fully vaccinated with the booster were included, regardless of time to covid-19 diagnosis.

All possibilities of reinforcement were considered:

-Full homologous booster dose:

A. 2 doses of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) with Pfizer-BioNTech booster

B. 2 doses of mRNA-1273 vaccine (Spikevax, formerly covid-19 Vaccine Moderna) with Moderna booster

-The 6 possible combinations of heterologous booster doses:

A. 2 doses of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) with mRNA-1273 vaccine booster (Spikevax, formerly covid-19 Vaccine Moderna)

B. 2 doses of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) with booster of mRNA-1273 vaccine (Spikevax, formerly covid-19 Vaccine Moderna)

C. 2 doses of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) with booster of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech)

D. 1 dose of Ad26.COV2.S (Janssen vaccine; Johnson & Johnson vaccine) with mRNA-1273 vaccine booster (Spikevax, formerly covid-19 Vaccine Moderna)

E. 1 dose of Ad26.COV2.S (Janssen vaccine; Johnson & Johnson vaccine) with booster of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech)

F. 2 doses of mRNA-1273 vaccine (Spikevax, formerly covid-19 Vaccine Moderna) with booster of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech)

4. Diagnosis of covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction (PCR) oropharyngeal swab tests or antigen testing. Rapid antigen tests began to be carried out for symptomatic patients with less than 5 days of evolution. The PCR tests were performed both in symptomatic patients and in asymptomatic contacts. The cases included confirmed cases and asymptomatic carriers. Information on covid-19 patients and their contacts was obtained from the registry systems used by general medical services in the consultation. A symptomatic confirmed case with active infection was considered to be any person with a clinical picture of sudden onset acute respiratory infection of any severity that occurs, among others, with fever, cough or feeling of shortness of breath. Other symptoms such as odynophagia, anosmia, ageusia, muscle pain, diarrhea, chest pain or headache, among others, were also considered symptoms of suspected SARS-CoV-2 infection according to clinical criteria; and a positive PCR or rapid antigen test positive [19, 21].

The onset date of a confirmed case was defined as the date of the first appearance of self-reported clinical symptoms [20]. The onset date for an asymptomatic carrier was defined as the date a positive covid-19 PCR test was obtained [22]. Previous SARS-CoV-2 infection was defined as a positive result in the PCR assay or antigen test at least 90 days before a new positive result [23].

Calculation of VBE [24-26] We calculated the VBE, which was estimated as a percentage [13, 24-26], as follows:

1- [Cases with vaccine booster shot <15 days / Cases with vaccine booster shot > = 15 days] × 100

Collected variables

The following variables were collected:

-Age and sex

-Chronic diseases (defined as "any alteration or deviation from normal that has one or more of the following characteristics: is permanent, leaves residual impairment, is caused by a non-reversible pathological alteration, requires special training of the patient for rehabilitation, and / or can be expected to require a long period of control, observation or treatment" [27], classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [28]

-Social-occupancy class (according to the Registrar General's classification of occupations and social status code) [29-30]

-If they were Health Care Workers

-Problems in the family context (complex families) based on the genogram and in the experience of the GP for their continuity of care and knowledge of the family (genogram is a schematic model of the structure and processes of a family, which included the family structure, life cycle and family relational patterns. It was understood that "complex" genograms present families with psychosocial problems) [31-34]

-Ethnic minority

-Vaccine type: Comirnaty (Pfizer-BioNTech-BNT162b2 mRNA; Pfizer / BioNTech), Moderna-mRNA-1273 mRNA, Vaxzevria (AstraZeneca), and Janssen / Johnson & Johnson vaccine (Currently, the European Commission has licensed four vaccines: Comirnaty, Pfizer / BioNTech, licensed December 21, 2020; Moderna vaccine, licensed January 6; AstraZeneca vaccine, licensed 29 December and the Janssen / Johnson & Johnson vaccine, authorized on March 11. In Spain, these four vaccines are currently available, all of which have been approved by the European Medicines Agency) [35]

Sample

All patients with covid-19 breakthrough infections in vaccinated people with vaccine booster at the consultation of general medicine for the period December 2021 to February 2022, were included.

Sample size

Sample size was calculated for two unpaired groups, with a Two-sided Confidence Level (1-alpha) of 95%, Power (% probability of detection) of 80%, Ratio of controls per case of 2:1, Proportion of covid-19 with exposure to 2 doses of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) plus mRNA-1273 vaccine (Spikevax, formerly covid-19 Vaccine Moderna) booster > = 15 days of 10%, and proportion of covid-19 with exposure to 2 doses of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) plus mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) booster < 15 days of 47%. The total sample size (Kelsey) had to be 45 (15 cases and 30 controls) [36].

Statistical analysis

The bivariate comparisons were performed using the Chi Square test (X2), X2 with Yates correction or Fisher exact test when necessary

(according to the number the expected cell totals), for percentages, and the Student test for the mean.

Results

Forty-six cases were included, 15 cases of covid-19 breakthrough infections in vaccinated people with vaccine booster shot <15 days (33%), with a time in days from booster to covid-19 (Arithmetic mean + - Standard deviation; Range) of 6.53+-3.31 (1-13 days), and 31 cases with vaccine booster shot > = 15 days (67%), with a time in days from booster to covid-19 of 37.41+-19.17 (15-84 days).

Cases with vaccine booster shot > = 15 days differed statistically from those with vaccine booster shot <15 days in having been vaccinated with 2 doses of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) plus mRNA-1273 vaccine (Spikevax, formerly covid-19 Vaccine Moderna) booster and less with 2 doses of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) plus mRNA-1273 vaccine (Spikevax, formerly covid-19 Vaccine Moderna) booster, having required more sick leave, presenting fewer digestive symptoms and fewer chronic skin diseases (TABLE 1 , TABLE2, TABLE3, TABLE 4).

VARIABLES	COVID-19 BREAKTHROUGH INFECTIONS <15 DAYS AFTER BOOSTER N=15	COVID-19 BREAKTHROUGH INFECTIONS > = 15 DAYS AFTER BOOSTER N=31	STATISTICAL SIGNIFICANCE
Age in years (Arithmetic mean + - Standard deviation; Range)	54.06+-12.40 (34-71 years)	53.61+-14.35 (26-90 years)	t= 0.10483. p= .458495. NS
> = 65 years	5 (33)	8 (26)	X2 with Yates correction= 0.0332. p= .855407. NS
= < 45 years	3 (33)	9 (29)	X2 with Yates correction= 0.0875. p= .767342. NS
Women	7 (47)	20 (65)	X2= 1.3284. p= .249082. NS
Previous symptomatic COVID-19	2 (13)	5 (16)	Fisher exact test=1. NS
Time in days from Booster to covid-19 in breakthrough infections in vaccinated people (Arithmetic mean + - Standard deviation; Range)	6.53+-3.31 (1-13 days)	37.41+-19.17 (15-84 days)	NR
Symptomatic covid-19 in breakthrough infections in vaccinated people	14 (93)	27 (87)	Fisher exact test=1. NS
Duration of symptoms in days of covid-19 in breakthrough infections in vaccinated people (Arithmetic mean + - Standard deviation; Range)	Symptomatic N=14 6.85+-2.56 (3-10 days)	Symptomatic N=27 5.29+-3.09 (2-15 days)	t= 1.61622. p= .057054. NS
Covid-19 breakthrough infections in vaccinated people with severity moderate and severe	1 (Pneumonia) (7)	0	Fisher exact test= 0.3261. NS
Social-occupancy class of patients (people with some type of labor specialization)	8 (53)	17 (55)	X2= 0.0092. p= .92345. NS
Health care workers with covid-19 breakthrough infections in vaccinated people	2 (13)	11 (35)	X2 with Yates correction= 1.4758. p= .224433. NS
Sick leave for covid-19 breakthrough infections in vaccinated people	3 (20)	17 (55)	X2= 4.9927. p= .025455. Significant at p < .05.
Ethnic minority with covid-19 breakthrough infections in vaccinated people	1 (7)	2 (6)	Fisher exact test=1. NS
Complex family with covid-19 breakthrough infections in vaccinated people	2 (13)	2 (6)	Fisher exact test statistic value is= 0.5868. NS
Chronic diseases presence in covid-19 breakthrough infections in vaccinated people	14 (93)	21 (68)	X2 with Yates correction= 2.368. p= .123843. NS

Table 1: *Covid-19 Breakthrough Infections <15 vs. > = 15 Days after Booster*

( ): Denotes percentages; NS: Not significant; NR: Not Relevant

SYMPTOMS * ACCORDING TO WHO, ICD-10 GROUPS	COVID-19 BREAKTHROUGH INFECTIONS <15 DAYS AFTER BOOSTER N=15	COVID-19 BREAKTHROUGH INFECTIONS > = 15 DAYS AFTER BOOSTER N=31	STATISTICAL SIGNIFICANCE
General (discomfort, asthenia, myalgia, fever, arthralgias)	12 (30)	22 (32)	X2= 0.0243. p= .87606. NS
Respiratory (cough, dyspnea, chest pain)	10 (26)	14 (20)	X2= 0.3731. p= .54134.
ENT (anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epixtasis)	12 (30)	29 (41)	X2= 1.422. p= .233073. NS
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	3 (7)	0	Fisher exact test = 0.0458. The result is significant at p < .05.
Neurological (headache, dizziness, mental confusion - brain fog)	3 (7)	5 (7)	Fisher exact test=1. NS
Total symptoms*	40 (100)	70 (100)	---

( ): Denotes percentages; NS: Not significant; *Patients could have more than one symptom. The percentages are over the total of symptoms

Table 2: *Symptoms in Covid-19 Breakthrough Infections <15 vs. > = 15 Days after Booster*

CHRONIC DISEASES* ACCORDING TO WHO, ICD-10 GROUPS	COVID-19 BREAKTHROUGH INFECTIONS <15 DAYS AFTER BOOSTER N=15	COVID-19 BREAKTHROUGH INFECTIONS > = 15 DAYS AFTER BOOSTER N=31	STATISTICAL SIGNIFICANCE
-II Neoplasias	1 (2)	4 (4)	Fisher exact test=1. NS
-III Diseases of the blood	0	1 (1)	Fisher exact test=1. NS
-IV Endocrine	7 (16)	17 (18)	X2= 0.1022. p= .749184. NS
-V Mental	3 (6)	5 (5)	Fisher exact test= 0.7104. NS
-VI-VIII Nervous and Senses	5 (11)	9 (9)	X2 with Yates correction= 0.0003. p= .98663
-IX Circulatory system	4 (9)	14 (14)	X2= 0.6502. p= .420056. NS
-X Respiratory system	3 (6)	5 (5)	Fisher exact test= 0.7104. NS
-XI Digestive system	6 (13)	12 (12)	X2= 0.0183. p= .892529. NS
-XII Diseases of the skin	6 (13)	2 (2)	X2 with Yates correction is 5.2781. p= .021595. Significant at p < .05.
-XIII Musculo-skeletal	6 (13)	11 (11)	X2= 0.0995. p= .75245. NS
-XIV Genitourinary	5 (11)	18 (19)	X2= 0.3887. p= .532984.
TOTAL chronic diseases*	46 (100)	98 (100)	---

( ): Denotes percentages; NS: Not significant; * Patients could have more than one chronic disease. The percentages are over the total of chronic diseases

Table 3: *Chronic Diseases in Covid-19 Breakthrough Infections <15 vs. > = 15 Days after Booster*

VACCINE TYPE	COVID-19 BREAKTHROUGH INFECTIONS <15 DAYS AFTER BOOSTER N=15	COVID-19 BREAKTHROUGH INFECTIONS > = 15 DAYS AFTER BOOSTER N=31	STATISTICAL SIGNIFICANCE
HOMOLOGOUS booster dose			
2 doses of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) with BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) booster	2 (13)	3 (10)	Fisher exact test= 0.6557. NS
2 doses of mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) with mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) booster	0	2 (6)	Fisher exact test= 0.5507. NS
HETEROLOGOUS booster dose			
2 doses of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) with mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) booster	5 (33)	20 (64)	X2= 3.9617. p= .046547. Significant at p < .05.
2 doses of ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca) with mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) booster	7 (47)	3 (10)	X2 with Yates correction= 6.1006. p= .013513. Significant at p < .05.
1 dose of Ad26.COV2.S (Janssen vaccine; Johnson & Johnson vaccine) with mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) booster	0	3 (10)	Fisher exact test= 0.5405. NS
2 doses of mRNA-1273 vaccine (Spikevax, formerly COVID-19 Vaccine Moderna) with BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) booster	1 (7)	0	Fisher exact test= 0.3261. NS
TOTAL	15 (100)	31 (100)	---

( ): Denotes percentages; NS: Not significant

Table 4: *Vaccine Type in Covid-19 Breakthrough Infections <15 vs. > = 15 Days after Booster*

Relative VBE <15 days vs. > 0 15 days [1 - (Cases with vaccine booster shot < 15 days) / (Cases with vaccine booster shot > = 15 days) x 100] was found to be 60%. (TABLE 5).

Cases with vaccine booster shot <15 days	GROSS INCIDENCE RATE	Cases with vaccine booster shot > = 15 days	GROSS INCIDENCE RATE
15/46	33%	31/46	67%

Relative vaccine booster effectiveness <15 days vs. > = 15 days:
1 - [Covid-19 cases incidence with vaccine Booster <15 days / Covid-19 cases incidence with vaccine Booster > = 15 days] × 100 = 60%

Table 5: *Relative Vaccine Booster Effectiveness > = 15 vs. <15 days*

Discussion

The turning points and waves of infections in the history of the covid-19 pandemic are marked by the mutation of the virus, that allow it to escape the first-line immune defences, specifically the antibodies; that is why breakthrough infections are seen in vaccinated people [37]. The omicron variant of SARS-CoV-2 began spreading rapidly and outpacing other variants in late 2021. Its broke records day after day, largely due to a series of mutations in the virus' spike protein that makes vaccines much less effective in stopping infection than in earlier variants [38-4].

Evidence of the high transmissibility of the omicron variant was corroborated by the rapid increase in reported covid-19 cases. In Spain during the so-called sixth wave in December 2021 and January 2022, this highly infectious strain of SARS-CoV-2 has brought covid-19 rates to the highest level ever seen [5, 41]. This situation triggered calls to intensify vaccination programs, including the provision of booster doses of the

vaccine [42]. However, neutralization of the omicron variant after the primary two-dose vaccine regimen was less than previous variants, but increased substantially after a booster dose [15]. Along these lines, it has been reported that the efficacy of mRNA vaccines to prevent hospital admissions associated with covid-19 was 86% for three doses against the omicron variant [13]. Other studies have observed a pronounced immune response after the third dose of BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) in people older than 60 years, against the Delta variant, a 33- and 51-fold increase in IgG and neutralizing antibodies, respectively; and neutralizing antibody levels after the third dose were 9.34-fold higher than after the second dose [2]. But on the other hand, another study reported an infection rate of 25% of participants in the three-dose control group being infected with the omicron variant, most with negligible symptoms. However, most infected participants were potentially infectious, with relatively high viral loads (nucleocapsid gene cycle threshold, ≤25). In addition, models from the University of Washington estimate that 90% of omicron cases will be asymptomatic compared to 40% for previous variants [43, 44].

In our study, the proportion of asymptomatic patients was very low both in cases of covid-19 with booster <15 days and >=15 days (7% and 13%, respectively), but it must be taken into account that were cases that consulted the GP, or infection was diagnosed after contact tracing, but no general screening activity was carried out. On the other hand, the symptoms presented by our patients were all mild, except for 1 pneumonia case, in the booster group < 15 days.

When does VBE drop?

Multiple time points have been used for VE assessment: ≥ 7 days (13, 45), from 10 to 14 days after shot (9), or at 2 to 4, 5 to 9, and 10 or more weeks after a booster [10]. VE is known progressively decrease over time since the primary vaccination series are completed. In this way, BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) and mRNA-1273 vaccine (Spikevax, formerly covid-19 Vaccine Moderna) booster shots have been reported to lose some effectiveness after four months [46]. Likewise, it has been published that for the ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford / AstraZeneca), BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech), or mRNA-1273 vaccine (Spikevax, formerly covid-19 Vaccine Moderna), the VE against Omicron progressively decreased to <15% after 25 weeks; this VE was also increased by immunization with the booster mRNA vaccine (all combinations). None of these three vaccines provide significant protection against symptomatic Omicron infection beyond 2 months after completion of the primary immunization series [10]. Neutralization titters against the omicron variant 6 months after the third (booster) dose of the vaccine were 6.3-fold lower than the maximum titters assessed 1 month after the booster injection [15].

A boost of BNT162b2 or mRNA-1273, after the primary course of ChAdOx1 nCoV-19 or BNT162b2, substantially increased the protection. But that protection decreased over time (10). With the current data, there is already evidence of a reduction in protection against symptomatic disease ten weeks after the booster dose, with a reduction in vaccine effectiveness from 15% to 25% after ten weeks [46]. It has been reported that binding antibody levels peaked at day 15 for the mRNA-boosted groups and were similar or decreased by day 29, while the levels of binding antibodies in the groups boosted with Ad26.COV2.S on day 29 were similar to or higher than those measured on day 15 [8].

Another study showed that the relative estimate of VE in the 14 days following the booster dose of BNT162b2 (Comirnaty, Pfizer-BioNTech), compared with people who received a two-dose primary course, was 87 in those who received two doses of ChAdOx1-S (Vaxzevria, AstraZeneca) as their main course and 84 in those who received two doses of BNT162b2 (Comirnaty, Pfizer-BioNTech) as their main course. Using the 2- to 6-day post-booster dose period as baseline yielded similar results [47].

The immune system has been reported to generate a large antibody response six to ten days later the booster dose against coronavirus [48].Our results suggest that BV received <15 days, compared with BV received >=15 days provided early protection against SARS-CoV-2 infection of symptomatic Covid-19 of 60%. At first glance, this result does not seem logical; The logical thing is to think that after 15 days from the booster, the effectiveness of the vaccine will be greater. These results are probably due to bias. Although this lower early risk has been observed in previous studies, it may be the result of different biases, especially "vaccination bias" [7, 49-51]. This effect has also been reported for the fourth dose [52]. For example, a systematic review of published studies has reported that after 7 days the vaccine effectiveness (VE) was 81%, after 14 days it was 80%, at 28 days it was 63%, at 42 days it was 93%, and after 56 days 93% [53]. This heterogeneity of results is mostly explained by the different types of vaccine received and "vaccinated bias." This bias is due to there is a greater propensity for healthier subjects to be more likely to be vaccinated than sick ones [54]. This bias can make the conclusions of observational studies erroneous [55]. In our study, "vaccination bias" may be the result of not including as cases with BV < 15 days some people who were already infected at the start of the study and, due to their symptoms, were less likely to choose to receive the vaccine on that specific day. In fact, in the same population of this study, the comparison the vaccine booster after a period of <29 days had relative VBE of 61% against symptomatic disease vs. <29 days [56], what seems more logical.

Are all covid-19 vaccine booster options the same?

In an evaluation of seven boosters, the BNT162b2 mRNA vaccine (Comirnaty, Pfizer / BioNTech) yielded the greatest escalation of antibody and cellular immune responses [57]. Based on data from the UK, immunity after the third dose is highly dependent on the combination of vaccines received. If the initial regimen has been with the Pfizer vaccine, a third dose also with Pfizer achieves 70% efficacy in preventing infections with symptoms in the first weeks after the booster. However, ten weeks after the booster dose with Pfizer, the efficacy in preventing infections with symptoms is reduced to 45%. In the event that the initial regimen has been with Pfizer and the booster dose with Moderna, the protection at the beginning is around 75% and remains stable above 70% nine weeks later. There is no data yet to know how long this protection will last. If the initial regimen has been with AstraZeneca, the protection in the first weeks after the third dose is around 60%. At nine weeks, it drops to 45% if Moderna has been received as a booster and to 35% if Pfizer has been received. For now, there are no data to evaluate the efficacy of other vaccine combinations - for example, if in the initial regimen has been received Moderna or Janssen [46, 58, 59]. In our study, the same type of mRNA vaccines was used in both the primary and booster series in most of the population, but the booster dose of mRNA-1273 was half the dose used in the primary series. Most boosters were heterologous. And the combination of 2 doses of Astra with Moderna booster had a higher EBV using <15-day post-booster period as baseline.

Limitations and strengths of the study

1. Non-randomized design, although by including all cases that were consulted with the GP, and taking into account the structure of the health system, the vast majority of cases were probably included.

2. Sample was small, so the statistical significance of some variables could be hidden, and an imprecise determination of vaccine effectiveness may be obtained.

3. It must be taken into account that the changes in community transmission during the study period may also imply changes in one

direction or another of the cautious behaviors and personal protection in people

4. May have been overlooked asymptomatic cases that did not attend in GP consultation, as no surveillance or systematic screening was done.

5. Estimates of omicron variant vaccine effectiveness were based on infections that occurred during periods when the omicron variant was in the majority, but genomic surveillance and classification were not performed. Consequently, this approach has the potential for variant misclassification.

6. VBE was studied only for a short period after the booster vaccination (December 2021 to February 2022), and there is no information on the duration of protection after a booster dose beyond this follow-up time.

Conclusion

Covid-19 vaccines showed excellent efficacy until the end of December 2021 when the world registered the highest number of infections related to the Omicron variant. On the other hand, it is not clearly known from what moment after the shot can it be considered effectiveness, and how long after the vaccine booster shot can be considered protective. In the context of the general medicine clinic in Toledo, Spain, from December 1, 2021 to February 28, 2022, in the peak period of omicron infections, the relative effectiveness of the homologous or heterologous booster vaccine, after a period of < 15 days vs. > = 15 days of the shot provided 60% protection against symptomatic disease. However, at first glance, this result does not seem logical; it should be the other way around. This lower early risk may be transitory and due to different biases, especially the "vaccinated bias"; This lower early risk has been observed in previous studies and may be the result of not including as "cases" (in our study, booster < 15 days) some people who were already infected at the beginning of the study and, due to their symptoms, they were less likely to choose to receive the vaccine on that specific day. Furthermore, our cohort was too small and the follow-up time too short to allow precise determination of vaccine effectiveness

References

1. Stokel-Walker C (2022) What do we know about covid vaccines and preventing transmission? BMJ; 376: o298.
2. Gilboa M, Mandelboim M, Indenbaum V, et al. (2022) Early Immunogenicity and Safety of the Third Dose of BNT162b2 Messenger RNA Coronavirus Disease 2019 Vaccine Among Adults Older Than 60 Years: Real-World Experience. J Infect Dis; 225(5): 785-792.
3. Kaku CI, Champney ER, Normark J, et al. (2022) Broad anti–SARS-CoV-2 antibody immunity induced by heterologous ChAdOx1/mRNA-1273 vaccination. Science; 375(6584): 1041-1047.
4. Kupferschmidt K, Vogel G (2022) Omicron cases are exploding. Scientists still don't know how bad the wave will be. Early data suggest the new variant may cause less severe disease and death-but hospitals are stretched to their limits. Science; 4 JAN.
5. Turabian JL (2022) Implications for general practitioner of evolution of incidence rates of COVID-19 breakthrough infections in vaccinated people as of December 2021 with the highest spike of infections of the entire pandemic. Arch Community Med Public Health; 8(1): 008-012.
6. Sablerolles RSG, Rietdijk WJR, Goorhuis A, et al. (2022) Immunogenicity and Reactogenicity of Vaccine Boosters after Ad26.COV2.S Priming. N Engl J Med.
7. Corrao G, Franchi M, Cereda D, et al. (2022) Persistence of protection against SARS-CoV-2 clinical outcomes up to 9 months since vaccine completion: a retrospective observational analysis in Lombardy, Italy. Lancet Infect Dis.
8. Atmar RL, Lyke KE, Deming ME, et al (2022) Homologous and Heterologous Covid-19 Booster Vaccinations. N Engl J Med.
9. Koelle K, Martin MA, Antia R, Lopman B, Dean NE (2022) The changing epidemiology of SARS-CoV-2. Science; 375(6585): 1116-1121.
10. Andrews N, Stowe J, Kirsebom F, et al. (2022) Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. N Engl J Med.
11. To KK, Hung IF, Ip JD, et al. (2021) Coronavirus Disease 2019 (COVID-19) Re-infection by a Phylogenetically Distinct Severe Acute Respiratory Syndrome Coronavirus 2 Strain Confirmed by Whole Genome Sequencing. Clin Infect Dis; 73(9): e2946-e51.
12. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, et al. (2022) Effect of mRNA Vaccine Boosters against SARS-CoV-2 Omicron Infection in Qatar. N Engl J Med.
13. Lauring AS, Tenforde MW, Chappell JD, et al. (2022) Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. BMJ; 376: e069761.
14. Grant B (2022) Editorial: When Will This Pandemic Officially End? The Scientst; Mar 11.
15. Pajon R, Doria-Rose NA, Shen X, et al (2022) SARS-CoV-2 Omicron Variant Neutralization after mRNA-1273 Booster Vaccination, N Engl J Med.
16. Nemet I, Kliker l, Lustig Y, et al. (2022) Third BNT162b2 Vaccination Neutralization of SARS-CoV-2 Omicron Infection. N Engl J Med; 386:492-494.
17. Turabian JL (1995) [Notebooks of Family and Community Medicine. An introduction to the principles of Family Medicine]. Madrid: Díaz de Santos.
18. CASE SERIES OF 46 COVID-19 BREAKTHROUGH INFECTIONS IN VACCINATED PEOPLE WITH VACCINE BOOSTER SHOT-Journal of Community and Preventive Medicine" --enviado el 15-3-22.
19. Ministerio de Sanidad (2021) [COVID-19 early detection, surveillance and control strategy. Updated December 1, 2021].
20. [Update 10 Vaccination strategy against COVID-19 in Spain. Recommendations agreed upon in the Public Health Commission after review and proposal made by the Vaccination Program and Registry Report together with the COVID-19 Vaccination Technical Working Group and the COVID-19 Vaccination Working Group in the Child Population December 2021].
21. Turabian JL (2022) Covid-19 Breakthrough Infections in Vaccinated People Versus Covid-19 Infections People without Vaccination: Secondary Data Analysis of Clinical-Epidemiological Characteristics in a General Medicine Practice in Toledo (Spain). J Community Prev Med; 4(2):23-31.
22. Mao S, Huang T, Yuan H, et al. (2020) Epidemiological analysis of 67 local COVID-19 clusters in Sichuan Province, China. BMC Public Health; 20: 1525.
23. Ayoub HH, Tomy M, Chemaitelly H, et al. (2022) Estimating protection afforded by prior infection in preventing reinfection: applying the test-negative study. MedRxiv 2022.01.02.22268622.
24. Martínez-Baz I, Trobajo-Sanmartín C, Miqueleiz A, et al. (2021) Product-specific COVID-19 vaccine effectiveness against secondary infection in close contacts, Navarre, Spain, April to August 2021. Euro Surveill; 26(39): pii=2100894.
25. Snijders BEP, van Lier A, van de Kassteele J, et al. (2012)

Mumps vaccine effectiveness in primary schools and households, the Netherlands, 2008. Vaccine; 30(19):2999-3002.
26. de Gier B, Andeweg S, Joosten R, et al. (2021) Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021. Euro Surveill;26(31):pii=2100640.
27. Strauss AL (1984) Chronic illness and the quality of life. St Louis: The C.V. Mosby Company.
28. WHO. International Statistical Classification of Diseases and Health-Related Problems. ICD-10 Version:2019.
29. Royal Collage of General Practitioners (1986) The Classification and Analysis of General Practice Data. Occasional Paper 26.
30. Donaldson RJ, Donaldson LJ (1983) Essential Community Medicine. Lancaster: MTP Press.
31. Turabian JL (2017) Family Genogram in General Medicine: A Soft Technology that can be Strong. An Update. Res Med Eng Sci. 3(1). RMES.000551.
32. Russell LT (2020) Capturing Family Complexity in Family Nursing Research and Practice. J Fam Nurs; 26(4):287-293.
33. Watts C, Shrader E (1998) How to do (or not to do). The genogram: a new research tool to document patterns of decision-making, conflict and vulnerability within households. Health Policy Plan; 13: 459-464.
34. McIlvain H, Crabtree B, Medder J, Stange KC, Miller WL (1998) Using practice genograms to understand and describe practice configurations. Fam Med; 30: 490-496.
35. Consejería de Sanidad Castilla La Mancha (2021).
36. Open Source Epidemiologic Statistics for Public Health.
37. McNamara D (2022) [Could the omicron wave hasten the transition from pandemic to endemic?]. Medscape; 6 de enero.
38. Robitzski D (2922) How Mild Is Omicron Really? Early reports that Omicron causes less-severe disease than Delta seem to be borne out, but it's not yet clear to what extent that's due to the variant itself versus the populations it's infecting. The Scientist; Jan 14.
39. Vanshylla K, Tober-Lau P, Gruell H, et al. (2022) Durability of omicron-neutralising serum activity after mRNA booster immunisation in older adults. Lancet Infect Dis.
40. Madhi SA, Kwatra G, Myers JE, et al. (2022) Population Immunity and Covid-19 Severity with Omicron Variant in South Africa. N Engl J Med.
41. Rae M (2022) Official list of covid-19 symptoms must be updated. BMJ; 376: o121.
42. Kuhlmann C, Mayer CK, Claassen M, et al. (2022) Breakthrough infections with SARS-CoV-2 omicron despite mRNA vaccine booster dose. Lancet;
43. Gray GE, Collie S, Garrett N, et al. (2021) Vaccine effectiveness against hospital admission in South African health care workers who received a homologous booster of Ad26.COV2 during an Omicron COVID19 wave: Preliminary Results of the Sisonke 2 Study. MedRxiv 2021.12.28.21268436.
44. Regev-Yochay G, Gonen T, Gilboa M, et al. (2022) Efficacy of a Fourth Dose of Covid-19 mRNA Vaccine against Omicron. N Engl J Med.
45. Moreira ED, Kitchin N, Xu X, et al. (2022) Safety and Efficacy of a Third Dose of BNT162b2 Covid-19 Vaccine. N Engl J Med.
46. 46.Ellis R (2022) Booster Effectiveness Wanes After 4 Months, Study Shows. Medscape; Feb 15,
47. Corbella J (2021) La protección de la tercera dosis frente a ómicron se reduce a las diez semanas. La Vanguardia; 24/12.
48. Andrews N, Stowe J, Kirsebom F, Gower C, Ramsay M, Lopez Bernal J (2021) Effectiveness of BNT162b2 (Comirnaty, Pfizer-BioNTech) COVID-19 booster vaccine against covid-19 related symptoms in England: test negative case-control study. BioRxiv 21266341.
49. Demonbreun AR, Sancilio A, Vaught LA, Reiser NL, Pesce L, McNally LM, et al. (2021) medRxiv2021.11.19.21266555.
50. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384:1412-1423.
51. Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. N Engl J Med 2021;385:1393-1400.
52. Mahmud SM, Righolt CH. Pitfalls of the healthy vaccinee effect. Lancet 2018;391:123-123.
53. Ori Magen, Jacob G. Waxman, Maya Makov-Assif, et al. (2022) Fourth Dose of BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med.
54. Ashmawy R, Hamdy NA, Elhadi YAM, et al. A Meta-Analysis on the Safety and Immunogenicity of Covid-19 Vaccines. Journal of Primary Care & Community Health. January 2022.
55. Eurich DT, Marrie TJ, Johnstone J, Majumdar SR. Mortality reduction with influenza vaccine in patients with pneumonia outside "flu" season: pleiotropic benefits or residual confounding? Am J Respir Crit Care Med 2008;178(5):527-533.
56. Alvear Téllez G (2013) Is there bias in the current recommendations for influenza vaccine? Medwave;13(10):e5848
57. Turabian JL (2022) Relative covid-19 vaccine booster effectiveness and clinical-epidemiological characteristics before and after 29 days of shot. Arch Pharmacol Ther. In Press.
58. Munro APS, Janani L, Cornelius V, et al. (2021) Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet.
59. Crist C (2021) COVID Booster Protection May Wane in About 10 Weeks, New Data Show. Medscape; Dec 27. Crist C (2021) COVID Booster Protection May Wane in About 10 Weeks, New Data Show. Medscape; Dec 27.
60. Segura A (2021) [Another (plausible) account of the pandemic is possible]. Salud, dinero y atención primaria: Viernes, 31 de Diciembre.